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(54) TITLE: Manufacturing method of 2-substituted adenosine derivative

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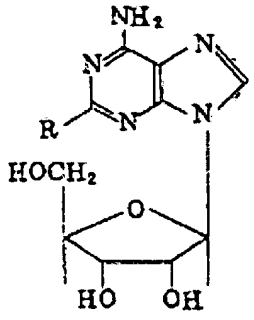
Detailed explanation of the invention

The present invention pertains to a method for manufacturing 2-substituted adenosine derivative. More specifically, the present invention pertains to a method for manufacturing 2-substituted adenosine derivative represented by the following general formula



[II]

(where, R represents hydrocarbon group or heterocyclic ring group), characterized by the fact that a reaction is carried out in the presence of a base between 5-amino-1-(β-D-ribofuranosyl)-4-imidazole carbonitrile and a nitrile compound represented by the following general formula

RCN [I]

(where, R has the same definition as described above).

In the conventional method for manufacturing 2-substituted adenosine derivative, 2',3'-isopropylidene-2-methylinosine obtained is treated with acetic anhydride. The obtained 2',3'-O-isopropylidene-5'-O-acetyl-2-methylinosine is processed into 2-methyl-6-chloro-9-(2',3'-O-

isopropylidene-5'-O-acetyl-β-D-ribofuranosyl) purine using phosphorous oxychloride. The compound obtained is treated with ammonia to obtain 2',3'-O-isopropylidene-2-methyl adenosine. Then, 2',3'-O-isopropylidene-2-methyl adenosine is treated with an acid to obtain 2-methyl adenosine ("Journal of Organic Chemistry" Vol. 33 (1968) p. 2583). However, this conventional method not only requires many complicated reaction steps, the yield of the targeted 2-methyl adenosine is also low. Besides, it is complicated to prepare 2',3'-O-isopropylidene-5'-O-acetyl-2-methylinosine used as the raw material. Therefore, this conventional method cannot be used as a satisfactory industrial manufacturing method.

The purpose of the present invention is to solve the aforementioned problem by providing a method that uses 5-amino-1-(β-D-ribofuranosyl)-4-imidazole carbonitrile as raw material and can manufacture adenosine derivative with 2- substituted by any hydrocarbon group or heterocyclic ring group by a simple one-step reaction.

The compound represented by said general formula (I) is used as the nitrile compound in the method of the present invention. R in the formula represents hydrocarbon group or heterocyclic ring group. Examples of the hydrocarbon group include methyl, ethyl, propyl, isopropyl, allyl, and other aliphatic hydrocarbon groups, phenyl, naphthyl, and other aromatic hydrocarbon groups, benzyl, phenethyl, and other aralkyl groups. Examples of heterocyclic ring group include furyl, thienyl, pyrrolyl, pyrazolyl, imidazoleyl, thiazolyl, oxazolyl, pyridyl, pyridazinyl, pyrimidinyl, triadinyl, etc. It is also possible to use condensed rings having the aforementioned rings in their molecules, such as indolyl and quinolyl, and the groups formed by bonding the aforementioned rings to aliphatic hydrocarbon groups, such as furfuryl. Also, these hydrocarbon groups or heterocyclic ring groups may have any substituent, such as halogen atom, nitro group, alkyl group, aryl group, haloalkyl group, hydroxyl group, alkoxy group, acyloxy group, thiol group, alkyl thio group, carboxylic acid, sulfonic acid, esters of these acids, amide, etc. at any position. It is preferred to use the nitrile compound [I] in equimolar amount or more with respect to 5-amino-1-(β-D-ribofuranosyl)-4-imidazole carbonitrile. In general, good result can be obtained if the itrile compound is used in the range of equimolar amount – 5-time molar amount.

In the method of the present invention, the reaction is carried out in the presence of a base between the aforementioned nitrile compound [I] and 5-amino-1-(β-D-ribofuranosyl)-4-imidazole carbonitrile. Examples of base that can be used include ammonia, methyl amine, dimethyl amine, or other amine, sodium methylate, sodium ethylate, sodium methoxy ethylate, potassium tertiary butyrate, or other sodium or potassium alcoholate. When the aforementioned

amines are used, these amines are used in equimolar amount or more with respect to 5-amino-1-(β-D-ribofuranosyl)-4-imidazole carbonitrile. It is also possible to use a solvent, such as methanol, ethanol, methyl cellosolve, or other alcohols, dimethyl formamide or dimethyl sulfoxide. In this case, it is usually preferred to carry out the reaction by heating the system to about 150-250°C under pressurization. The reaction is usually completed within 20 h.

If the aforementioned alcoholates are used as the base, the amount can be in the range of equimolar amount – 5-time molar amount with respect to 5-amino-1-(β-D-ribofuranosyl)-4-imidazole carbonitrile. In this case, good result can be obtained by performing reflux under heating for about 10-48 h in an alcohol solvent, such as methanol, ethanol, tertiary butanol, methyl cellosolve, etc.

The generated adenosine derivative [II] with 2- substituted by the heterocyclic ring group or hydrocarbon group supplied by the nitrile compound [I] can be easily collected from the reaction solution. For example, the reaction solution can be concentrated directly or after it is neutralized, followed by recrystallization from water, etc. In this way, the 2-subsittued adenosine derivative [II] can be separated and purified easily.

The 2-substituted adenosine derivatives [II] obtained using the method of the present in vention include novel compounds that are not disclosed in references. These compounds can improve blood flow in coronary [artery] and can lower blood pressure with significant continuity compared with adenosine.

The 2-substituted adenosine derivative [II] can be obtained easily at high yield by using the method of the present invention. Therefore, the present invention has a very high industrial value.

In the following, the present invention will be explained in more detail with reference to application examples.

Application Example 1

970 mg of 5-amino-1-(β-D-ribofuranosyl)-4-imidazole carbonitrile (referred to as AICN-riboside hereinafter), 1.2 g of benzonitrile, and 32 mL of 20% methanol-based ammonia were mixed and heated at 180°C for 15h in a sealed tube. After cooled off, the reaction solution was concentrated under reduced pressure, followed by adding 5 mL of ethanol into the remaining substance to deposit crystal. The crystal was then filtered and recrystallized from water,

obtaining 353 mg (yield 36%) of colorless needle-shaped crystal of 2-phenyl adenosine. The melting point was in the range of 228-229°C.

Element analyzing values

Calculated values as $C_{16}H_{17}O_4N_5$:

C 55.97 ; H 4.99 ;

N 20.40

Experimental values: C 55.63 ; H 4.86 ;

N 20.43

$[\alpha]_D^{28} = -0.3°$ (C = 1.0, dimethyl formamide)

UV absorption spectrum

$\lambda_{max}^{0.1\,N-HCl}$ 270 mμ (ε 16200),

294 mμ (shoulder-shaped absorption)

$\lambda_{max}^{H_2O}$ 238.5 mμ (ε 23400),

268 mμ (ε 14300)

$\lambda_{max}^{0.1\,N-NaOH}$ 238.5 mμ (ε 24100),

268 mμ (ε 14300)

Application Example 2

1.15 g of metal sodium was dissolved in 100 mL of ethanol, followed by adding 2.4 g of AICN-riboside and 2.06 g of benzonitrile. The system was heated under reflux for 16 h. After the end of the reaction, the reaction solution was poured into 100 mL of water, followed by adding 1 N hydrochloric acid to adjust pH to 6. After the solution was concentrated to 30 mL under reduced pressure, it was set at a cold place. As a result, 1.03 g of colorless crystal of 2-phenyl adenosine was obtained.

Application Example 3

1.2 g of AICN-riboside, 815 mg of 4-nitrobenzonitrile, and 30 mL of 20% methanol-based ammonia were mixed and heated at 200°C for 15 h in a sealed test tube. The process after that was carried out in the same way as described in Application Example 1, obtaining 745 mg (yield 38% of yellow needle-shaped crystal of 2-(4-nitrophenyl) adenosine. The melting point was 265°C.

Element analyzing values

Calculated values as $C_{16}H_{16}O_6N_6$:

C 49.50 ; H 4.15 ;

N 21.64

Experimental values: C 49.65 ; H 4.08 ;
N 21.53

$(\alpha)_D^{19} = +7.5°$ (C=1.0, dimethyl formamide)

UV absorption spectrum

$\lambda_{max}^{0.1N-HCl}$ 264 mμ (ε 15500),
315 mμ (ε 13.200)

$\lambda_{max}^{H_2O}$ 217.5 mμ (ε 22400),
262 mμ (ε 17400) , 318 mμ (ε
11200)

$\lambda_{max}^{0.1N-NaOH}$ 220.5 mμ (ε 20.700),
263 mμ (ε 16900) , 320 mμ (ε
10200)

Application Example 4

10 g of AICN-riboside, 12.5 g of 2-cyanofuran, and 100 mL of 20% methanol-based ammonia were mixed and heated at 180°C for 14 h in a sealed test tube. The process after that was carried out in the same way as described in Application Example 1, obtaining 7.85 g (yield 55%) of colorless crystal of 2-(2-furyl) adenosine. The melting point was in the range of 135-140°C.

Element analyzing values

Calculated values as $C_{14}H_{15}O_5N_5 \cdot \frac{1}{2}H_2$:
C 49.12 ; H 4.71 ;
N 20.47

Experimental values: C 49.38 ; H 4.54 ;
N 20.49

$(\alpha)_D^{22} = -38.9°$ (C=1.0, dimethyl formamide)

UV absorption spectrum

$\lambda_{max}^{0.1N-HCl}$ 214 mμ (ε 19000),
284 mμ (ε 14800) , 317 mμ (ε
20500) ,

$\lambda_{max}^{H_2O}$ 252 mμ (Shoulder-shaped absorption) , 258 mμ
(ε 18800), 286 mμ (Shoulder-shaped absorption) ,
299 mμ (ε 19400)

$\lambda_{max}^{0.1N-NaOH}$ 252 mμ (Shoulder-shaped absorption) ,
258 mμ (ε 18800), 286 mμ
(Shoulder-shaped absorption) , 299 mμ (ε 19200)

(Shoulder-shaped absorption)

Application Example 5

2.4 g of AICN-riboside, 3.5 g of 2-cyanothiophene, and 50 mL of 20% methanol-based ammonia were mixed and heated at 180°C for 15 h in a sealed test tube. The process after that was carried out in the same way as described in Application Example 1, obtaining 2.016 g (yield 58%) of colorless crystal of 2-(2-thienyl) adenosine. The melting point was 250°C.

Element analyzing values

Calculated values as $C_{14}H_{15}O_4N_5S$:

C 48.13 ; H 4.33 ;
N 20.04 ; S 9.18

Experimental values:

C 48.01 ; H 4.33 ;
N 20.10 ; S 9.25

$[\alpha]_D^{25} = -18.7°$ (C=1.0, dimethyl formamide)

UV absorption spectrum

$\lambda_{max}^{0.1N-HCl}$ 212 mμ (ε 20900), 273 mμ (ε 12700), 323 mμ (ε 15900)

$\lambda_{max}^{H_2O}$ 253 mμ (ε 16600), 306 mμ (ε 15400)

$\lambda_{max}^{0.1N-NaOH}$ 252 mμ (ε 17200), 307 mμ (ε 15500)

Application Example 6

240 mg of AICN-riboside, 114 mg of 4-cyanopyridine, and 8 mL of 20% methanol-based ammonia were mixed and heated at 180°C for 15 h in a sealed test tube. The process after that was carried out in the same way as described in Application Example 1, obtaining 174 mg (yield 50%) of colorless needle-shaped crystal of 2-(4-pyridyl) adenosine. The melting point was 300°C.

Element analyzing values

Calculated values as $C_{15}H_{16}O_4N_8$:

C 52.32 ; H 4.68 ;
N 24.41

Experimental values:

C 52.18 ; H 4.66 ;
N 24.45

$[\alpha]_D^{25} = -4.1°$ (C=1.0, dimethyl formamide)

UV absorption spectrum

$\lambda_{max}^{0.1N-HCl}$ 246 mμ (ε 18900), 270 mμ (ε 12700), 332 mμ (ε 6900)

$\lambda_{max}^{H_2O}$ 233.5 mμ (ε 23800), 268 mμ (ε 13500), 305 mμ (Shoulder-shaped absorption)

$\lambda_{max}^{0.1N-NaOH}$ 234 mμ (ε 24200), 268 mμ (ε 14000), 305 mμ

(Shoulder-shaped absorption)

Application Example 7

240 mg of AICN-riboside, 114 mg of 3-cyanopyridine, and 8 mL of 20% methanol-based ammonia were mixed and heated at 180°C for 15 h in a sealed test tube. The process after that was carried out in the same way as described in Application Example 1, obtaining 126 mg (yield 37%) of colorless crystal of 2-(3-pyridyl) adenosine. The melting point was in the range of 269-270°C.

Element analyzing values

Calculated values as $C_{15}H_{16}N_6O_4$:

C 52.32 ; H 4.68 ;
N 24.41

:Experimental values: C 52.29 ; H 4.56 ;
N 24.95

$[\alpha]_D^{20} = -6.0°$ (C=0.4, dimethyl formamide)

UV absorption spectrum

$\lambda_{max}^{0.1N-HCl}$ 238 mμ (ε 18900), 260 mμ (ε 14700), 303 mμ (ε 7600)

$\lambda_{max}^{H_2O}$ 233 mμ (ε 24000), 263 mμ (ε 14000), 292 mμ (Shoulder-shaped absorption)

$\lambda_{max}^{0.1N-NaOH}$ 233 mμ (ε 23900), 263 mμ (ε 13800), 282 mμ

(Shoulder-shaped absorption)

Application Example 8

240 mg of AICN-riboside, 114 mg of 2-cyanopyridine, and 8 mL of 20% methanol-based ammonia were mixed and heated at 180°C for 15 h in a sealed test tube. The process after that was carried out in the same way as described in Application Example 1, obtaining 164 mg (yield 46.5%) of colorless crystal of 2-(2-pyridyl) adenosine. The melting point was in the range of 148-150°C.

Element analyzing values

Calculated values as $C_{15}H_{16}O_4N_6 \cdot \frac{1}{2}H_2O$

C 50.99 ; H 4.85 ;
N 23.79

Experimental values: C 51.26 ; H 4.59 ;
N 23.55

$[\alpha]_D^{23} = -49.1°$ C=0.93, dimethyl formamide)

UV absorption spectrum

$\lambda_{max}^{0.1\,N-HCl}$ 233mμ (ε 15200), 263 mμ (ε 13500), 328 mμ (ε 8300)

$\lambda_{max}^{H_2O}$ 231.5mμ (ε 20900), 262 mμ (ε 13800), 290 mμ (ε 9900)

$\lambda_{max}^{0.1\,N-NaOH}$ 231.5 mμ (ε 20800), 262 mμ (ε 13700), 289 mμ (ε 9800)

Application Example 9

1.5g of AICN-riboside, 1.5 mL of acetonitrile, and 30 mL of 20% methanol-based ammonia were mixed and heated at 180°C for 16 h in a sealed test tube. After cooled off, the reaction solution was concentrated under reduced pressure, the remaining substance was dissolved in methanol, followed by adding chloroform to deposit the crystal. The crystal was then filtered and recrystallized from water, obtaining 950 mg of colorless needle-shaped crystal of 2-methyl adenosine.

Element analyzing values

Calculated values as $C_{11}H_{15}N_5O_4 \cdot \frac{1}{2}H_2O$:

C 45.55 ; H 5.56 ;
N 24.12

Experimental values: C 45.64 ; H 5.20 ;
N 24.17

UV absorption spectrum
$\lambda_{max}^{0.1N-HCl}$ 258 mμ ,
$\lambda_{max}^{H_2O}$ 262 mμ ,
$\lambda_{max}^{0.1N-NaOH}$ 262 mμ

Application Example 10

1 g of AICN-riboside, 1 g of para-methoxybenzonitrile, and 15 mL of 20% methanol-based ammonia were mixed and heated at 180°C for 16 h in a sealed test tube. The reaction solution was treated in the same way as described in Application Example 1, obtaining 0.5 g of colorless needle-shaped crystal of 2-(4-methoxyphenyl) adenosine. The melting point was 250°C.

Element analyzing values
Calculated values as $C_{17}H_{19}O_5N_5$:
C 54.68 ; H 5.13 ;
N 18.76
Experimental values: C 54.48 ; H 5.12 ;
N 18.78

UV absorption spectrum
$\lambda_{max}^{H_2O}$ 253 mμ , 289 mμ
$\lambda_{max}^{0.1N-HCl}$ 274 mμ , 306 mμ

Application Example 11

1 g of AICN-riboside, 1.2 g of 3,4,5-trimethoxybenzonitrile, and 20 mL of 20% methanol-based ammonia were mixed and heated at 180°C for 20 h in a sealed test tube. The reaction solution was treated in the same way as described in Application Example 1, obtaining 0.52 g of colorless needle-shaped crystal of 2-(3,4,5-trimethoxyphenyl) adenosine. The melting point was in the range of 99-101°C.

Element analyzing values
Calculated values as: $C_{19}H_{23}O_7N_5 \cdot \frac{1}{4}H_2O$
C 51.57 ; H 5.47 ;
N 15.83

Experimental values: C 51.41 ; H 5.41 ;
N 16.19

UV absorption spectrum
$\lambda_{max}^{H_2O}$ 221 mμ , 261 mμ , 295 mμ

Application Example 12

1.5 g of AICN-riboside, 1.0 g of propionitrile, and 20 mL of methanol-based sodium methylate were mixed and heated at 180°C for 16 h in a sealed test tube. The reaction solution was treated in the same way as described in Application Example 1, obtaining 0.5 g of powder of 2-ethyl adenosine.

Element analyzing values
Calculated values as: $C_{12}H_{17}H_5O_4 \cdot ¼H_2O$:
C 48.07 ; H 5.88 ;
N 23.36
Experimental values: C 48.10 ; H 5.77 ;
N 23.31

UV absorption spectrum
$\lambda_{max}^{0.1N-HCl}$ 260 mμ (ε 14000),
$\lambda_{max}^{H_2O}$ 264 mμ (ε 14400),
$\lambda_{max}^{0.1N-NaOH}$ 264 mμ (ε 15300)

Application Example 13

1.5 g of AICN-riboside, 2 g of valelonitrile, and 30 mL of methanol-based sodium methylate were mixed and heated at 180°C for 16 h in a sealed test tube. The reaction solution was treated in the same way as described in Application Example 1, obtaining 0.4 g of powder of 2-butyl adenosine.

Element analyzing values
Calculated values as $C_{14}H_{21}N_5O_4 \cdot ⅓H_2O$:
C 50.59 ; H 6.67 ;
N 21.07
Experimental values: C 50.63 ; H 6.34 ;
N 20.82

N. M. R. (In d_6-DMSO) .
δ(ppm) : 1.10 (3H , t , CH_3-)
1.3 - 2.1 (4H , m ,
$-CH_2-CH_2-$)
2.8 (2H , m , $-CH_2-$) , 6.0
(1H , d , H_1)
7.25 (2H , broad S , $-NH_2$)
8.15 (1H , S , H_8)

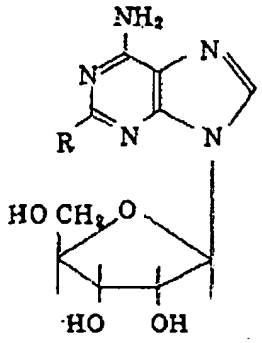
Application Example 14

1.5 g of AICN-riboside, 4.0 g of para-chlorobenzonitrile, and 20 mL of 20% methanol-based ammonia were mixed and heated at 180°C for 20 h in a sealed test tube. The reaction solution was treated in the same way as described in Application Example 1, obtaining 1.8 g of light yellow needle-shaped crystal of 2-(4-chlorophenyl) adenosine. The melting point was 258°C.

Element analyzing values
Calculated values as $C_{16}H_{16}N_5O_4Cl$:
C 50.87 ; H 4.27 ;
N 18.54
Experimental values: C 50.41 ; H 4.25 ;
N 17.92

CLAIM

1. A method for manufacturing 2-substituted adenosine derivative represented by the following general formula



(where R represents hydrocarbon group or heterocyclic ring group), characterized by the fact that a reaction is carried out in the presence of a base between 5-amino-1-(β-D-ribofuranosyl)-4-imidazole carbonitrile and a nitrile compound represented by the general formula RCN (where R has the same definition as described above).

Manufacturing method of 2-substituted adenosine derivative

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